b1

Claim 1. (amended) An effervescent pharmaceutical formulation for the sustained and controlled oral administration of a pharmaceutically effective amount of a drug selected from a calcium channel blocker, an ACE inhibitor, a narcotic analgesic or analogues or combinations thereof, said formulation comprising microcapsules having a D50% between about 100 nm and 900 nm in which the drug is entrapped in a biodegradable polymer and in which the pH of the formulation is adjusted to optimize delivery of the drug, wherein the formulation is adapted to disperse upon addition of water to form an effervescent drink.

Please delete Claims 2 and 4 without prejudice.

Please add the following new claims:

b2

Claim 21. (new) The effervescent pharmaceutical formulation of Claim 1, wherein the drug is diltiazem or a combination of diltiazem and a narcotic analgesic or an ACE inhibitor and wherein the pH of the formulation is greater than 7.

Claim 22. (new) The effervescent pharmaceutical formualtion of Claim 1, wherein the drug is hydromorphone or a combination of hydromorphone and a calcium channel blocker or an ACE inhibitor and wherein the pH of the formulation is less than pH 6 or greater than pH 7.

REMARKS

Claims 1, 3, and 5-22 are pending in this application. Claim 1 has been amended, Claims 2 and 4 have been deleted without prejudice and new Claims 21 and 22 have been added. Support for the amendment to Claim 1 and the addition of new Claims 21 and 22 can be found throughout the specification such as at originally filed Claims 2 and 4, page 3, lines 15-31 and Example 14. Thus, applicant submits that no new matter has been added by this Amendment.

Rejection under 35 U.S.C. § 103 (a)

The Examiner has rejected Claims 1-20 as being unpatentable under 35 U.S.C. § 103(a) over Wheling et al. (US 5,178,878) and Wong et al. (US 4,824,675).

In particular, the Examiner states that Wheling et al. show oral microcapsular dosage forms comprising an analgesic pharmaceutical agent, an effervescent disintegration agent and a polymeric protective material. The claims differ in reciting a particular combination of actives, plus use of a particular polymer.

The Examiner further states than Wong et al. teach particles or granules comprising polylactide, an effervescent couple, and an active agent selected from analgesics, antagonists, calcium and channel inhibitors. The Examiner concludes that since Wehling et al. disclose the conventionality of dosage forms such as that claimed, it would have been obvious to employ the microparticles of '878 by selecting polylactide polymer in conjunction with nifedipine, diltiazem, capropril, analgesics or mixtures thereof to obtain the known and expected combination of benefits.

The applicants respectfully traverse this rejection.

The subject matter as presently claimed in the present application is drawn to an effervescent formulation which is designed for ingesting as an effervescent drink and which has both controlled and sustained release characteristics. That is, the combination of (1) entrapping the drug in a biodegradable polymer to form microcapsules and (2) adjusting the pH of the effervescent formulation provides a drug release profile from the effervescent drink that not only optimizes delivery of the drug to a particular site or sites of absorption but also allows effective treatment over a predetermined extended period of time, such as once-daily. Additionally, the drug is encapsulated in particles having a size of D50% between about 100 nm and 900 nm. Thus, upon additon of water, the particles are dispersed to produce a fine suspension. As noted on page 3, lines 25 to 31, because this uniform suspension is formed prior to the subject ingesting the effervescent drink, the effect of food, presence of bile, pH etc. upon the dissolution of the dosage form is minimized, allowing for improved reproducibility of dosing.

Wheling et al. ('878) describe a pharmaceutical dosage form that incorporates microparticles which are susceptible to rupture upon chewing or which are adapted to provide substantially immediate relase of the pharmaceutical ingredient contained in the microparticles. These microparticles are provided in a

tablet adapted for direct oral administration with an effervescent disintegration agent.

Contrary to the present invention, '878 describes and claims dosage forms that contain microparticles having a size between about 75 and 600 microns (*see*, e.g., Claims 4, 5, 8, 9 and Col. 9, line 64 to Col. 10, line 2). '878 teaches rapid release particles, such as 70% release of the pharmaceutical ingredient within 30 minutes, that typically are relatively fragile and relatively prone to rupture and/or other types of pharmaceutical ingredient release in the patient's mouth (*see*, e.g., Col. 3, lines 12-39). In direct contrast, the present invention claims much smaller particles having a D50% between about 100 nm and 900 nm for a sustained, such as once-daily, and controlled oral administration of the drug.

Additionally, '878 teaches or suggests only a tablet adapted for direct oral administration so that the effervescent disintegration agent can provide an effervescent sensation in the mouth of the patient to provide a "positive" organoleptic sensation. The tablets of '878 should disintegrate in the mouth of a patient in less than 10 minutes and desirably between about 30 seconds and 7 minutes. As described in '878, the combination of rapid release microparticles and the effervescent disintegration agent provides an oral dosage form which offers both immediate release and effective taste-masking. In contrast and as discussed above, the instant invention employs effervescent excipients to form a uniform suspension of particles having sustained and controlled release characteristics (an effervescent drink) prior to the subject ingesting the drink to allow for improved reporducibility of dosing.

Contrary to the instant invention, nowhere does '878 attempt to optimize a sustained and controlled delivery of the pharmaceutical ingredient to a particular site or sites of absorption.

The '878 is meant to solve oral administration problems distinct from those solved in the instant invention. As such, nowhere does '878 teach, disclose or suggest to one skilled in the art an effervescent pharmaceutical formulation for sustained and controlled release of the drug from nanoparticles having a D50% between about 100 nm and 900 nm in which the pH of the formulation is adjusted to optimize delivery of the drug and in which the formulation is adapted to disperse

upon addition of water to form an effervescent drink prior to ingestion by the patient. Indeed, because the '878 teaches the rapid release of a pharmaceutical ingredient from microparticles sized from about 75 to 600 microns upon direct oral administration of a tablet containing these microparticles and an effervescent disintegrating agent , '878 teaches away from the instantly claimed invention.

The combination of Wong et al. ('675) with '878 does not render the instant invention obvious. The principle object of '675 is to provide a dispenser comprising novel means for the controlled delivery of a beneficial agent at a rate substantially equivalent to its dispense~~d~~r controlled rate of release from the dispenser over time (*see*, e.g., Col 2, lines 31 to 36). As described by '675 in Col. 2, the dispenser comprises a reservoir ~~the~~ compris~~ed~~ing a plurality of tiny pills such that the dispenser delivers the tiny pills at a controlled rate in a fluid environment of use as a tiny-timed-pill carrier is rate displaced from the dispenser. Nowhere does the complicated dispenser of '675 disclose the use of an effervescent agent to form an effervescent drink prior to ingestion by the patient (that is, prior to delivery to the fluid environment of use). Further, selection of particular active agents or particular "tiny pill" wall-forming agents from the extensive lists of these elements provided in '675 for incorporation in the fast-release tablet adapted for direct oral administration of '878 does not disclose, teach or suggest the instantly claimed invention.

Thus, neither '878 or '675, taken either singly or combined, render the instant invention unpatentable. As such, the applicants believe that all claims are nonobvious over either '878 or '675 and respectfully requests that the Examiner withdraw all the outstanding rejections under 35 U.S.C. § 103.

The applicants acknowledge the Examiner's citation of US 5,500,227 as being of interest.

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

The Commissioner is authorized to charge $950.00 to Deposit Account No. 05-0670 as required for the extension of time. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 05-0670.

Respectfully submitted,

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on this 16th day of April, 1998.

Mary L. Severson — April 16, 1998
Mary L. Severson — Date